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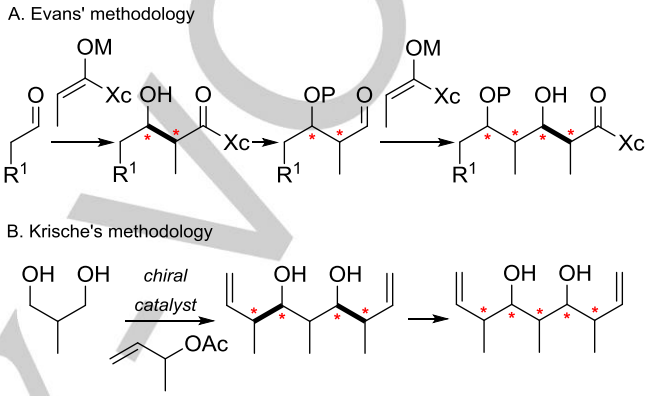
Stereocontrolled synthesis of polypropionate fragments based on a building block assembly strategy using lithiation-borylation methodologies

Alba Millán,[a] Pablo D. Grigol Martínez[a] and Varinder K. Aggarwal*[a]

Dedication ((optional))

Abstract: Polypropionates are important structural motifs in nature and are commonly made by iterative aldol or crotylation methodologies. Herein, we present an alternative strategy in which stereochemically predefined building blocks bearing appropriate functionality are coupled together using lithiation-borylation methodology with complete stereocontrol. The building blocks comprise lithiated carbamates acting as donors and boronic esters acting as acceptors. The acceptor building blocks contain β-hydroxyl groups masked as silyl groups to avoid elimination of the boronate intermediates. Subsequent oxidation of both the boron and silyl moieties can then deliver an array of polypropionate fragments with full stereochemical control, including the synthetically challenging *anti–anti* isomers.



Scheme 1. Evans´and Krische´s synthesis of polypropionates

Introduction

Amongst all the classes of natural products, the polyketides are arguably the most important due to their broad spectrum of biological activities spanning antibiotic, antitumor, antifungal, antiparasitic and immunomodulatory.[1,2] Their biological importance, coupled with their structural complexity has made them attractive targets for synthetic chemists for decades.[3] Indeed, the synthesis of highly complex polyketide natural products using Evans' methodology[4] has been one of the major achievements in organic synthesis of the 20th century. Recently Krische's group developed a catalytic crotylation reaction, wherein two-directional chain growth can be used to rapidly construct polypropionate fragments[5] (Scheme 1). Other notable methods include Leighton's tandem carbonylative crotylations which similarly reduces step count with high efficiency.[6,7] However, these methods often require redox processes between iterative chain extension steps which increase the step count. Furthermore, assembly of the carbon chain by introducing one propionate unit at a time occasionally leads to difficulties in accessing certain stereoisomers due to matched/mis-matched effects caused by substrate bias.[8]

We have considered an alternative approach in which small, stereodefined building blocks are coupled together using our lithiation-borylation methodology[9] in a fully stereocontrolled manner. The development of such an approach, which is demonstrated in this paper, has significant potential because it would (i) allow the synthesis of any stereoisomeric polypropionate motif with fully predictable stereochemistry (ii) enable the synthesis of non-natural analogues which can display improved therapeutic profiles.

Platform Design: In order to develop a systematic approach based on small and easy-to-prepare building blocks, we identified two key sub-structural motifs that would enable the synthesis of a diverse set of polypropionates (Scheme 2A). These motifs are the donor **D** (primary carbamate or benzoate), and the acceptor **A** (chiral boronic esters, ***Si*** = $SiMe_2Ph$). By assembling these building blocks stereoselectively a broad range of stereopentads (five contiguous stereogenic centres) can potentially be prepared. Crucially, the exquisite reagent-control of stereoselectivity displayed by lithiation-borylation will enable access to all possible diastereoisomers.

Building Block Design: While the design of building blocks **D** is aimed at ease of synthesis and protecting group orthogonality, the element of design for building block **A** is critical. Ideally, building block **A** would contain an O-based group β to the Bpin group. However, the lithiation-borylation of such boronic esters is usually not possible because they undergo E2 elimination instead of the required 1,2-metallate rearrangement[10] (Scheme 2B). By using a β-silicon-containing boronic ester this problem is alleviated as the silyl group serves as a masked O-functionality that cannot act as a leaving group, which will enable the desired 1,2-migration to take place.

[a] Dr. A. Millán, Dr. P. D. G. Martínez, Prof. Dr. V. K. Aggarwal
School of Chemistry
University of Bristol
Cantock's Close, Bristol, BS8 1TS, UK
E-mail: V. Aggarwal@bristol.ac.uk.

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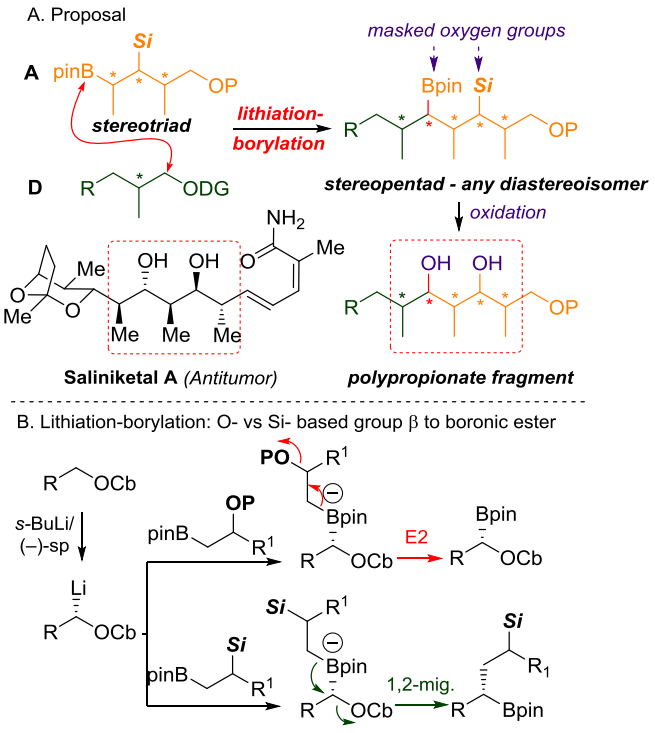


Scheme 2. Proposed strategy for the synthesis of polypropionate fragments. pin = pinacolato, *Si* = $PhMe_2Si$; Cb = *N*,*N*-diisopropylcarbamoyl; sp = sparteine.

Furthermore, since natural polypropionates contain an array of ether, ester and alcohol functionalities, methods for the differentiation of the various hydroxyl groups are required. As such, the use of a silyl group as a masked O-functionality is further advantageous because it allows additional discrimination between this group and the numerous other protected hydroxyl groups.

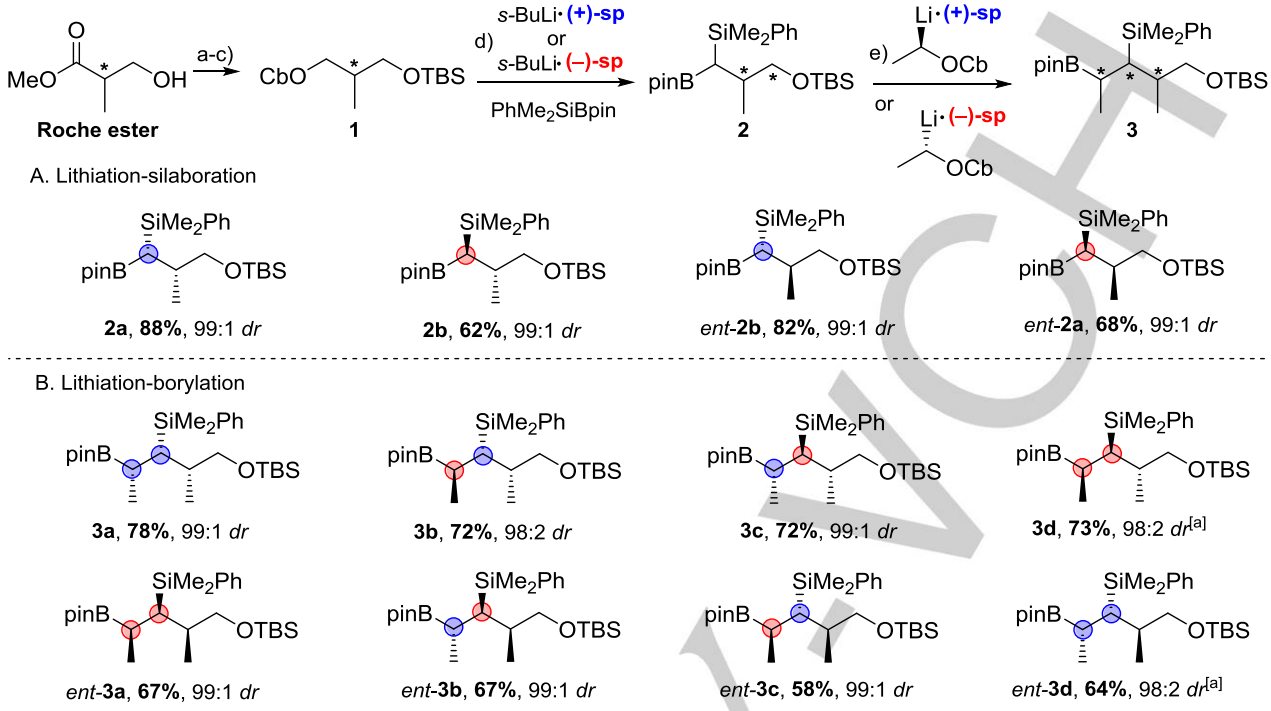
Results and Discussion

We commenced our studies with the synthesis of the acceptor building block **3**, accomplished by two consecutive lithiation-borylation reactions (Scheme 3). Starting with commercially available Roche ester, the corresponding carbamate **1** was prepared by TBS protection,[11] ester reduction and carbamoylation of the primary alcohol. This carbamate **1** was submitted to the first lithiation-borylation reaction using commercially available $PhMe_2SiBpin$[12] to give the corresponding *gem*-silaboronic ester **2** with high diastereocontrol[13] By combining both enantiomers of the Roche ester and both enantiomers of sparteine, all four *gem*-silaboronic ester stereoisomers **2** were obtained in good yields and excellent diastereoselectivities, showing that no matched or mis-matched effects were operative. Subsequent homologation with lithiated ethyl carbamate gave a complete set of the eight possible stereoisomeric building blocks (4 diastereomers and their enantiomers, Scheme 3) of the corresponding stereotriads **3** in good yield and excellent diastereocontrol. In the case of compound **3d** and *ent*-**3d** a modified protocol for the final homologation was required. Under standard conditions (*s*-BuLi, (+)- or (–)-sp), the boronate complex was not formed efficiently (as determined by ^{11}B NMR), possibly due to steric hindrance. In order to decrease the steric hindrance of the lithiated carbenoid, exchange of the hindered sparteine ligand for the less hindered TMEDA was carried out, as described by O'Brien.[14] Therefore, after lithiation with *s*-BuLi/(+)- or (–)-sparteine was completed (5h), TMEDA was added followed by the boronic ester and subsequent warming to room temperature. Under these conditions, boronate complex formed and, after migration, compound **3d** and *ent*-**3d** were obtained in good yields and excellent diastereoselectivities. Using this methodology, rapid access to all possible stereotriads in good yield and excellent diastereoselectivities was achieved, providing a useful platform for polypropionate synthesis.

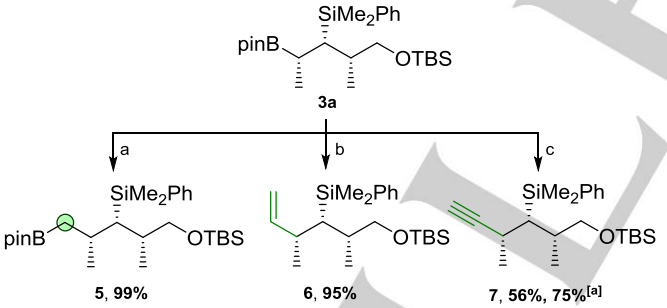
The boronic ester present in **3** is a versatile functional group for chemical diversification[15] and, as a result, is a useful synthon in synthesis. This was briefly demonstrated by conducting Matteson homologation,[16] Zweifel olefination[17] and alkynylation reactions[18] (Scheme 4), which all proceeded in good yields and diastereospecificity (>95%).

The stereotriad building blocks could be further elongated into stereotetrads using our lithiation-borylation methodology. To illustrate this, a simple carbamate **8** was used in combination with two different diastereomeric stereotriads **3a** and **3c** using (+)- and (–)-sparteine. This gave the corresponding stereotetrads **9a**-**9d** in excellent yield and, again with very high stereocontrol in every case (Scheme 5), including the challenging *anti-anti-anti* stereoisomer **9c**, which is sometimes difficult to prepare by aldol or crotylation reactions due to mis-matched effects.[19]

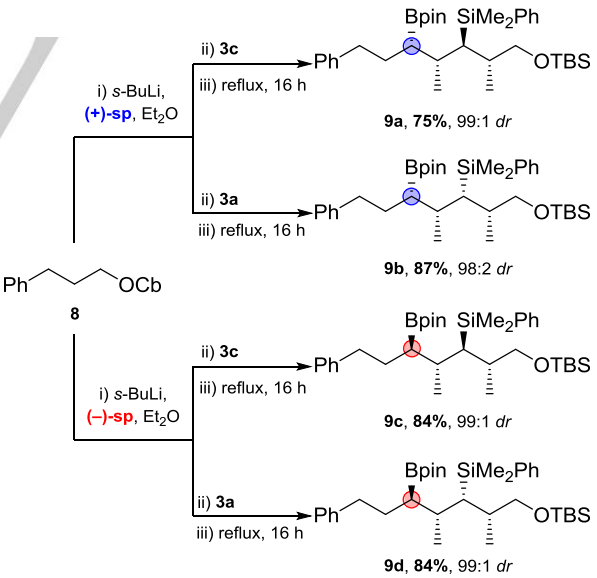
Having constructed stereotriads and stereotetrads we move towards the synthesis of stereopentads through the reaction of stereotriads **3** with β-methyl substituted carbamates or TIB esters. Although lithiation-borylation reactions have been widely employed in late stage synthesis of natural products, usually relatively non-hindered boronic esters or lithiated carbenoids have been employed.[20] We anticipated that this reaction, involving two hindered coupling partners (**10**/**11** and **3**, Table 1), might be challenging due to the formation of highly congested ate-complexes and the complications associated with the subsequent 1,2-migration of such species. We started our investigation using the corresponding TIB ester **10** (entry 1). Under these conditions the desired product **14a** was obtained in low yield. Analysis by ^{11}B NMR revealed that following full boronate complex formation (δ_B = 7 ppm), an equimolar mixture of boronic and borinic esters were obtained (δ_B = 32 ppm and 52 ppm respectively) in the subsequent 1,2-migration. This result showed that O-migration competed with C-migration. We have previously found that the balance between O- vs C-migration can be influenced by the nature of the leaving group [21] and so explored the use of carbamate **11** in place of the TIB ester **10** (entry 2). Pleasingly, selective 1,2-C-migration was now



Scheme 3. Stereoselective synthesis of stereotriads **3**. Conditions: a) TBSCl (1.4 eq.), imidazole (2.4 eq.), DMAP (0.12 eq.), DCM, rt, 2 h; b) DIBAL-H (2.2 eq.), THF, –78 °C, 2 h, rt, 30 min; c) Cb-Cl (1.5 eq.), Et_3N (1.5 eq.), DCM, 40 °C, 48 h; d) i) *s*-BuLi (1.3 eq.), (+)- or (–)-sp (1.3 eq.), Et_2O, –78 °C, 5 h; ii) $PhMe_2Si$-Bpin (1.3 eq.), –78 °C, 1.5 h; iii) rt, 16 h; e) i) Ethyl carbamate (2 eq.), *s*-BuLi (2 eq.), (+)- or (–)-sp (2 eq.), Et_2O, –78 °C, 5 h; ii) **2** (1 eq.), –78 °C, 1.5 h; iii) rt, 16 h. [a] Modified conditions e) were used: i) Ethyl carbamate (2 eq.), *s*-BuLi (2 eq.), (+)- or (–)-sp (2 eq.), Et_2O, –78 °C, 5 h; ii) TMEDA (4 eq.), –78 °C, 1 h; iii) **2** (1 eq.), –78 °C, 1.5 h; iv) rt, 16 h. Diastereoselectivity was determined by GC-MS and/or ^{1}H-NMR analysis of crude material.

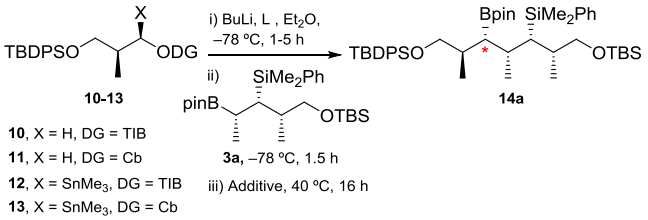


Scheme 4. Transformations of stereotriad **3a**. [a] Yield based on recovered starting material. Conditions: a) Bromochloromethane (3 eq.), *n*-BuLi (2 eq.), Et_2O, –78 °C, 30 min, rt, 1 h; b) i) vinylmagnesium bromide (4 eq.), THF, rt, 30 min; ii) I_2 (4 eq.), MeOH, –78 °C, 30 min; iii) MeONa (8 eq.), MeOH, –78 °C to rt, 1 h; c) i) vinyl bromide (2 eq.), LDA (2 eq.), Et_2O, –95 °C, 1 h; ii) I_2 (2.2 eq.), MeOH, –95 °C, 5 min, rt, 1 h; iii) work up; iv) LDA (2.5 eq.), THF, –78 °C to rt, 1 h.



Scheme 5. Stereoselective synthesis of stereotetrads **9a**-**9d**. General conditions: **8** (1.3 eq.), *s*-BuLi (1.3 eq.), (+)- or (–)-sp (1.3 eq.), Et_2O, –78 °C, 5 h; ii) **3a** or **3c** (1 eq.), –78 °C, 1.5 h; iii) 40 °C, 16 h. Diastereoselectivity was determined by GC-MS analysis of crude material.

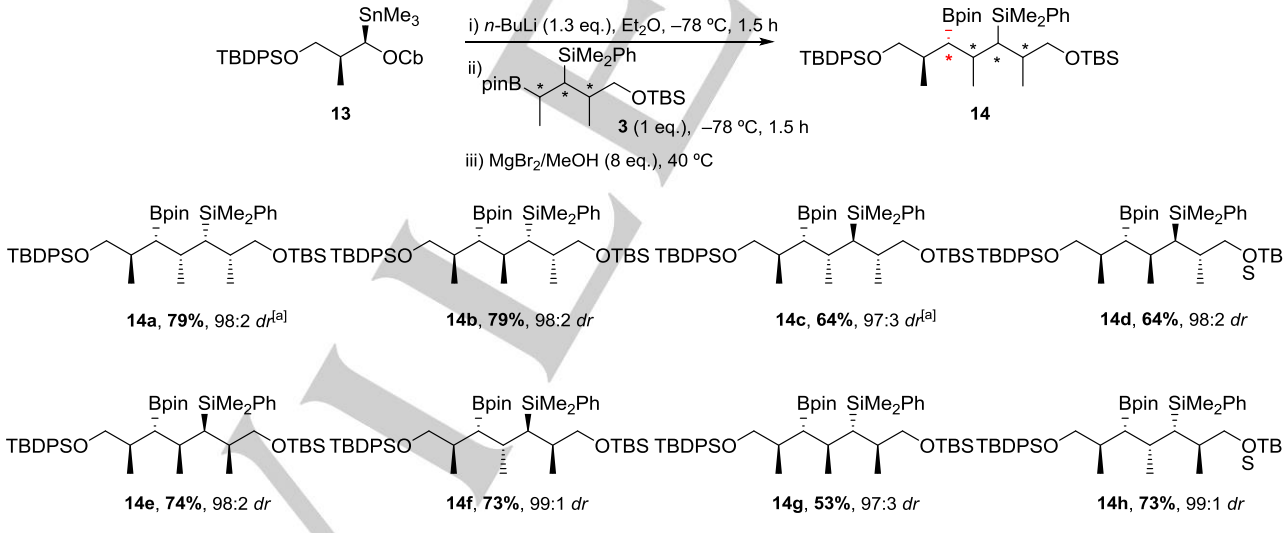
Table 1. Optimisation of lithiation-borylation reaction for synthesis of steropentads.



Entry	Compound	Ligand (L)	Additive	Yield (%)[a]	C-mig:O-mig[b]
1	**10**	(+)-sp	-	36	50:50
2	**11**	(+)-sp	-	25	100:0
3	**12**	-	-	36	50:50
4	**13**	-	-	40	100:0
5	**13**	-	$MgBr_2{\cdot}Et_2O$	51	100:0
6	**13**		$MgBr_2$/MeOH	79	100:0

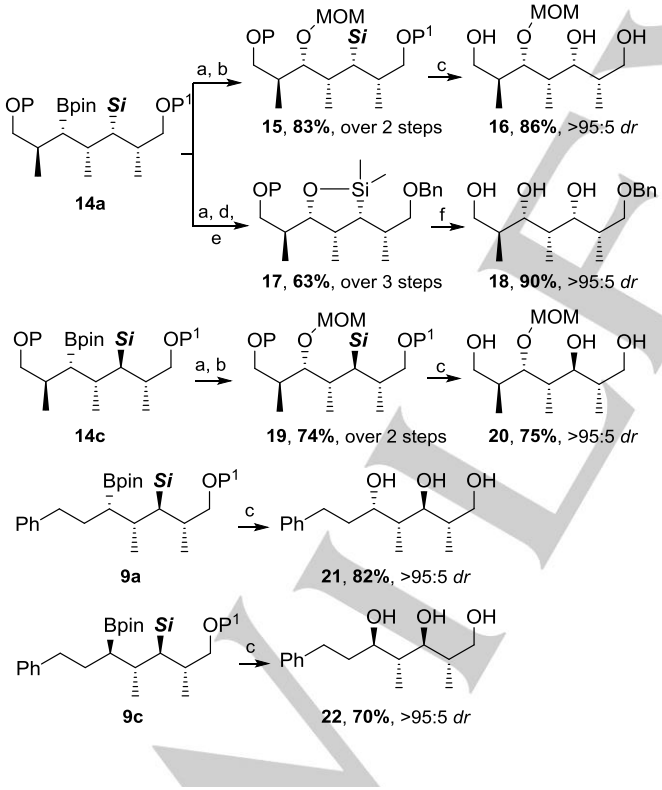
[a] Yield of **14a** after purification. [b] C-migration:O-migration ratio determined by ^{11}B NMR. Conditions: **10**-**13** (1.3 eq.), *s*- or *n*-BuLi (1.3 eq.), L (1.3 eq.), Et_2O, –78 ºC, 1-5 h; ii) **3a** (1 eq.), –78 ºC, 1.5 h; iii) additive (8 eq.), –78 ºC to 40 ºC, 16 h. TIB = 2,4,6-triisopropylbenzyl.

observed, although still in low yield. Diamine-free conditions have been found to promote reactions between lithiated carbamates/TIB esters and hindered boronic esters.[21b,22] However, when the reaction was attempted using the stannyl TIB ester **12** (entry 3) a comparable result to entry 1 was obtained. Encouragingly, the corresponding stannyl carbamate **13** (entry 4), gave the desired product, without competing O-migration, although in low yield (40%), with recovery of the starting boronic ester **3a** (51%). Since boronate complex was formed completely, the return of the starting boronic ester **3a** must come from fragmentation of the boronate complex back to its constituent parts. An attempt to promote 1,2-migration using $MgBr_2{\cdot}OEt_2$[23] (entry 5) was marginally successful (51%), although boronic ester **3a** was still recovered (46%). Improved results were obtained using $MgBr_2$/MeOH (entry 6), a system that we have previously used to promote 1,2-migration at the expense of reversibility back to starting materials.[24] Under these conditions, the desired stereopentad **14a** was obtained in 79% yield with excellent diastereoselectivity (98:2 *dr*) and all of the boronic ester **3a** was consumed. We further confirmed the reversible nature of the ate-complex by adding a second boronic ester ($PhCH_2CH_2Bpin$) to the reaction mixture after step ii) and observing products arising from the reaction of both boronic esters under conditions similar to entry 5.[25] With the optimised conditions in hand, we applied the methodology to the building blocks **3** synthesised in Scheme 3. The reactions proceeded smoothly with *all eight stereoisomers*, giving the desired compounds in good yields (51-79%) and excellent diastereoselectivities, greater than 97:3 *dr* in every case (Scheme 6). Furthermore, this reaction proved to be highly robust, scalable and easy to purify.



Scheme 6. Stereoselective synthesis of stereopentads **14**. General procedure: i) **13** (1.3 eq.), *n*-BuLi (1.3 eq), Et_2O, –78 °C, 1.5 h; ii) **3** (0.08 mmol, 1 eq.), –78 °C, 1.5 h; iii) $MgBr_2$/MeOH (8 eq.), –78 °C to 40 °C, 16 h. Diastereoselectivity was determined by ^{1}H-NMR analysis of the crude material and/or purified compound. [a] Reaction carried out in 1 mmol scale.

Having constructed the carbon backbone with full stereocontrol, the last step required selective oxidation of the boron and silyl moieties to reveal the polypropionate motifs (Scheme 7). The stereospecific oxidation of the boronic esters[26] was achieved in excellent yields using standard conditions (H_2O_2, NaOH, THF). However, the oxidation of the C–Si bond proved much more challenging. No oxidation occurred under standard and modified Fleming-Tamao conditions,[27,28] but by using a modified Woerpel oxidation[29] protocol (NaH, *t*-BuOOH, TBAF, DMF) the desired polypropionate fragments **16**, **20**, **21** and **22** were obtained in excellent yields. In order to demonstrate the potential for orthogonality, the secondary alcohol, obtained after C–B oxidation, was protected as a MOM ether (**15** and **19**) and subsequently oxidised to the triols **16** and **20**. In addition, after initial C–B bond oxidation of compound **14a**, selective deprotection of the TBS group, followed by simultaneous formation of a cyclic alkoxysilane[30] and protection of the primary alcohol as a benzyl ether was carried out. For alkoxysilane **17**, a water free Tamao oxidation, using H_2O_2-urea complex, was also successful. Furthermore, oxidation of both the silyl and boronic ester moieties could be carried out directly after the lithiation-borylation reaction, as demonstrated in the case of stereotetrads **9a** and **9c**, which gave the corresponding triols **21** and **22** in good yields.



Scheme 7. Oxidation of C–B and C–Si bonds. P= TBDPS, P^1=TBS, ***Si***= $PhMe_2Si$. Conditions: a) 30% H_2O_2, 2 M NaOH, THF, 0 °C to rt, 2 h; b) MOM-Cl (2 eq.), DIPEA (3 eq.), DCM, 0 °C to rt, 16 h; c) NaH (6 eq.), *t*-BuOOH (6 eq.), TBAF (2 eq.), DMF, 70 °C, 16 h; d) 1% HCl, EtOH, rt, 2 h; e). NaH (2.2 eq.), THF, 0 °C, 30 min then BnBr (2.2 eq.), 0 °C to rt, 14 h; f) H_2O_2-urea (15 eq.), $KHCO_3$ (6 eq.), KF (11 eq.), DMF, 70 °C, 16 h.

Conclusions

In this study, we have designed a stereotriad boronic ester building block bearing a masked-hydroxy silyl substituent that can serve as useful platform for the synthesis of an array of stereopentads. Coupling of the stereotriads with chiral lithiated-carbamates using lithiation-borylation methodology leads to the creation of short chain polypropionate fragments after oxidation of the masked groups. This methodology is highly robust and versatile as *any stereochemical outcome* can be achieved just by changing the chiral ligand employed in the key coupling step. Importantly, the high level of reagent-control of stereochemistry provided by the lithiated-carbamates prevented any matched/mismatched effects and resulted in uniformly excellent diastereoselectivities. Furthermore, conditions were established for the coupling of hindered boronic esters with hindered carbamates, thereby further extending the scope of this useful methodology.

Experimental Section

Experimental procedures are presented in the Supporting Information.

Acknowledgements

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Keywords: polypropionate • stereo-*n*-ads • diastereoselectivity • lithiation-borylation • silaboration

[1] a) M. T. Davies-Coleman, M. J. Garson, *Nat. Prod. Rep.***1998**, *15*, 477; b) A. M. P. Koskinen, K. Karisalmi, *Chem. Soc. Rev.* **2005**, *34*, 677; c) C. Hertweck, *Angew. Chem. Int. Ed.* **2009**, *48*, 4688; *Angew. Chem.* **2009**, *121*, 4782.

[2] a) J. Rohr, *Angew. Chem. Int. Ed.* **2000**, *39*, 2847; *Angew. Chem.* **2000**,*112*, 2967; b) S. Omura, *Macrolide antibiotics. Chemistry, biology and practice*, Elsevier, New York, **2002**; c) F. E. Koehn, G. T. Carter, *Nat. Rev. Drug Discov*. **2005**, *4*, 206.

[3] a) K. Zheng, C. Xie, R. Hong, *Front. Chem.* **2015**, 3:32, 1; b) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100,* 2407.

[4] D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, J. Bartroli*, Pure Appl. Chem.* **1981**, *53*, 1109.

[5] a) A.-M. R. Dechert-Schmitt, D. C. Schmitt, X. Gao, T. Itoh, M. J. Krische, *Nat. Prod. Rep.* **2014**, *31*, 504; b) J. Feng, Z. A. Kasun, M. J. Krische, *J. Am. Chem. Soc.* **2016**, *138*, 5467; c) S. W. Kim, W. Zhang, M. J. Krische, *Acc. Chem. Res.* **2017**, *50*, 2371.

[6] a) T. J. Harrison, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 7308; b) S. Ho, C. Bucher, J. L. Leighton, *Angew. Chem. Int. Ed.* **2013**, *52*, 6757; *Angew. Chem.* **2013**, *125*, 6889; c) C. N. Foley, J. L. Leighton, *Org. Lett.* **2014**, *16*, 1180; d) L.-A. Chen, M. A. Ashley, J. L. Leighton, *J. Am. Chem. Soc.* **2017**, *139*, 4568.

[7] For other notable examples see: a) I. Paterson, V. A. Doughty, M. D. McLeod, T. Trieselman, *Angew. Chem. Int. Ed.* **2000**, *39*, 1308; Angew.

Chem. **2000**, *112*, 1364; b) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, N. Sereinig, *J. Am. Chem. Soc.* **2001**, *123*, 9535; c) K. A. Scheidt, A. Tasaka, T. D. Bannister, M. D. Wendt, W. R. Roush, *Angew. Chem. Int. Ed.* **1999**, *38*, 1652; *Angew. Chem.* **1999**, *111*, 1760; d) M. Chen, W. R. Roush, *J. Org. Chem.* **2013**, *78*, 3; e) J. R. Dunetz, L. D. Julian, J. S. Newcom, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 16407; f) M. W. Andersen, B. Hildebrandt, R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 97; g) R. Sturmer, K. Ritter, R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 101; h) H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570.

[8] a) M. Turks, M., S. Laclef, P. Vogel in *Construction of Polypropionate Fragments in Natural Product Synthesis. Stereoselective Synthesis of Drugs and Natural Products*, ed. Wiley, Germany, **2013**; b) D. Menche, J. Li, *Synthesis* **2009**, 2293; c) B. Schetter, R. Mahrwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7506; *Angew. Chem.* **2006**, *118*, 7668.

[9] a) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem. Int. Ed*. **2007**, *46*, 7491; *Angew. Chem.* **2007**, *119*, 7635; b) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778; c) D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174. The methodology is based on the Hoppe lithiation of carbamates: d) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282; e) E. Beckmann, V. Desai, D. Hoppe, *Synlett* **2004**, 2275.

[10] a) D. Matteson, *J. Organomet. Chem.* **1999**, *581*, 51; b) E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 165.

[11] When methoxymethyl acetal (MOM ether) was used as protecting group, lower diastereoselectivity was observed in the lithiation-silaboration reactions (~90:10 *dr*) probably due to chelation effects.

[12] M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647.

[13] V. K. Aggarwal, M. Binanzer, M. Carolina de Ceglie, M. Gallanti, B. W. Glasspoole, S. J. F. Kendrick, R. P. Sonawane, A. Vazquez-Romero, M. P. Webster, *Org. Lett.* **2011**, *13*, 1490.

[14] a) M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun*. **2006**, 2607; b) M. J. McGrath, P. O'Brien, *Synthesis* **2006**, *13*, 2233; c) M. J. McGrath, P. O'Brien, *J. Am. Chem. Soc.* **2005**, *127*, 16378; d) G. Carbone, P. O'Brien, G. Hilmersson, *J. Am. Chem. Soc.* **2010**, *132*, 15445; e) J. L. Bilke, P. O'Brien, *J. Org. Chem.* **2008**, *73*, 6452.

[15] C. Sandford, V. K. Aggarwal, *Chem. Commun*. **2017**, *53*, 5481.

[16] a) K. M. Sadhu, D. S. Matteson, *Organometallics* **1985**, *4*, 1687; b) D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 1529; c) H. C. Brown, T. Imai, P. T. Perumal, B. Singaram, *J. Org. Chem.* **1985**, *50*, 4032; d) For a review see: D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555.

[17] a) G. Zweifel, H. Arzoumanian, C. C. Whitney, *J. Am. Chem. Soc.* **1967**, *89*, 3652; b) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2011**, *50*, 3760; *Angew. Chem.* **2011**, *123*, 3844; c) For a review see: R. J. Armstrong, V. K. Aggarwal, *Synthesis* **2017**, *49*, 3323.

[18] Y. Wang, A. Noble, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 4270; *Angew. Chem.* **2016**, *128*, 4342.

[19] a) R. W. Hoffmann, D. Dahmann, M. W. Andersen, *Synthesis* **1994**, 629; b) B. Cheng, D. Trauner, *J. Am. Chem. Soc.* **2015**, *137*, 13800; c) M. Chen, W. R. Roush, *J. Am. Chem. Soc.* **2012**, *134*, 3925; d) C. Allais, P. Nuhant, W. R. Roush, *Org. Lett.* **2013**, *15*, 3922. See also reference 6a.

[20] a) A. P. Pulis, P. Fackler, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 4382; *Angew. Chem.* **2014**, *126*, 4471; b) R. Rasappan, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 810; c) S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398; d) C. A. Brown, V. K. Aggarwal, *Chem. Eur. J.* **2015**, *21*, 13900; e) A. Millán, J. R. Smith, J. L.-Y. Chen, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 2498; *Angew. Chem.* **2016**, *128*, 2544 ; f) A. Noble, S. Roesner, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 15920; *Angew. Chem.* **2016,** *128*, 16152; g) A. Varela, L. K. B. Garve, D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 2127; *Angew. Chem.* **2017**, *129*, 2159; h) J. Wu, P. Lorenzo, S. Zhong, M. Ali, C. P. Butts, E. L. Myers, V. K. Aggarwal, *Nature* **2017**, *547*, 436.

[21] a) For Br/Cl in Matteson homologations see ref. 15b; b) For TIB/Cb in lithiation-borylation: D. J. Blair, C. J. Fletcher, Katherine M. P. Wheelhouse, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 5552; *Angew. Chem.* **2014**, *126*, 5658.

[22] a) A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 14663; *Angew. Chem.* **2016**, *128*, 14883; b) D. J. Blair, D. Tanini, J. M. Bateman, H. K. Scott, E. L. Myers, V. K. Aggarwal, *Chem. Sci.* **2017**, *8*, 2898.

[23] M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 4025.

[24] a) V. Bagutski, R. M. French, V. K. Aggarwal, *Angew. Chem. Int. Ed*. **2010**, *49*, 5142; *Angew. Chem.* **2010**, *122*, 5268; b) S. Roesner, D. J. Blair, V. K. Aggarwal, *Chem. Sci.* **2015**, *6*, 3718.

[25] This experiment was carried out using equimolar amount of **13**, **3a** and *n*-BuLi followed by $PhCH_2CH_2Bpin$ and adding $MgBr_2{\cdot}OEt_2$ as additive. We observed full boronate complex formation after addition of the first boronic ester **3a** and obtained a 2:1 ratio of products arising from reaction with **3a** and $PhCH_2CH_2Bpin$ respectively. See ESI for details.

[26] a) H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 2544; b) D. S. Matteson in *Stereodirected synthesis with organoboranes*, Springer, Berlin, **1995**; pp. 48-119.

[27] G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599.

[28] See ESI for further details.

[29] J. H. Smitrovich, K. A. Woerpel, *J. Org. Chem.* **1996**, *61*, 6044. Conditions described in this reference for the oxidation of SiR_3 failed in our case (eg. *t*-BuOOH, KH, NMP, 70 °C or *t*-BuOOH, KH, TBAF, NMP, 70 °C). A change of solvent (DMF) together with the presence of TBAF was crucial for the efficient oxidation of the silyl group.

[30] T. Harada, S. Imanaka, Y. Ohyama, Y. Matsuda, A. Oku, *Tetrahedron Lett.* **1992**, *33*, 5807.

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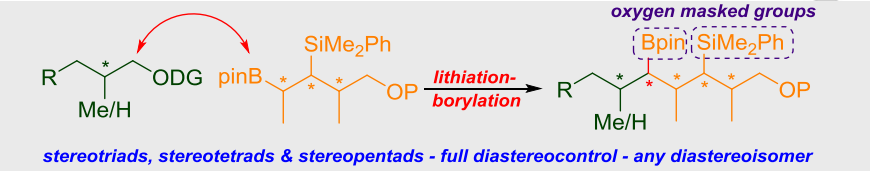

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Stereocontrolled synthesis of polypropionate fragments based on a building block assembly strategy using lithiation-borylation methodologies

Any stereochemical outcome for short chain polypropionate fragments has been achieved by assembly of carbamates and β-silaboronic esters via lithiation-borylation reactions. Stereotriads, tetrads and pentads are obtained in good yields and excellent diastereoselectivity under reagent-control conditions.